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EXAMINER	
SGAGIAS, MAGDALENE K	

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1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/789,247	LU ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/2/07*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,6-8,11,14,17,18 and 20-37* is/are pending in the application.

4a) Of the above claim(s) *20-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 6-8, 11, 14, 17-18, 32-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 7/2/07 have been fully considered but they are not persuasive. The amendment has been entered. Claims 1, 3, 6-8, 11, 14, 17-18, 20-37 are pending. Claims 20-31 are withdrawn. Claims 2, 4-5, 9-10, 12-13, 15-16, 19, are canceled. Claims 1, 3, 6-8, 11, 14, 17-18, 32-37 are under consideration.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 6-8, 11, 17-18 rejection under 35 U.S.C. 102(b) is withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 6-8, 11, 14, 17-18 rejection under 35 U.S.C. 103(a) is withdrawn.

Applicant's arguments with respect to claims 1, 3, 6-8, 11, 14, 17-18, have been considered but are moot in view of the new ground(s) of rejection.

Claims 1, 3, 6, 17, 32, 34, are rejected under 35 U.S.C. 103(a) as being unpatentable over **Gonczol et al,** (US 6,448,389 B1; 2002) in view of **Mach et al,** (Journal of Virology, 11881-11892, 2000); **Temperton** (International Journal of Antimicrobial Agents, 19: 169-172, 2002).

Gonczol et al, teach a composition comprising of DNA plasmids encoding different human CMV (HCMV) polypeptides such as glycoprotein B (gB), gB transmembrane deleted derivatives, pp65, pp150 for in vitro and in vivo expression of these plasmids (abstract). Gonczol teaches methods of using the DNA plasmids to induce immune responses to HCMV and provides a series of HCMV genome fragments, which are particularly useful in inducing a HCMV-specific immune responses (column 1, lines 54-57). Gonczol teaches a composition comprising a plurality of sets of nucleic acid molecules, encoding a different type of cytomegalovirus (CMV) polypeptide, and each molecule of a set encoding the same type of CMV polypeptide, wherein a plasmid pTet-gB, containing the portion of the HCMV genome (UL55) encoding gB. This plasmid further contains a tetracycline regulatable HCMV-immediate early promoter (column 1, lines 65-67; column 2, lines 1-4). Gonczol et al, teaches a plasmid encoding the full-length gB subunit protein is a pΔRC-gB and another plasmid pΔRC-gB_{680}, containing the portion of the human CMV (HCMV) genome encoding the N-terminal 680 amino acids of the gB protein (column 2, lines 5-10). Gonczol et al, also teaches a pΔRC-pp65 plasmid which contains the portion of the HCMV genome (UL83) encoding the HCMV pp65 tegument protein and the pΔRC-pp150 plasmid which contains the portion of the HCMV genome (UL32) encoding the HCMV pp150 tegument protein (column 2, lines 10-15). Gonczol et al, further teaches of six mice inoculated with the pΔRC-pp65 alone at a single site, 3 mice responded with the pp65-specific lysis of target cells (figure 2) and in another experiment 3 of nine mice immunized with the pΔRC-pp65 alone showed strong pp65-sepcific CTL responses and CTL responses were also detected in 4 of 5 mice inoculated with a mixture of pΔRC-pp65

and pTet-gB. Gonczol et al, teaches a preparation of a pharmaceutically acceptable immunogenic composition, having appropriate pH, isotonicity, stability and other conventional characteristics, wherein the recombinant plasmid is suspended in isotonic water, phosphate buffered saline, or the like (wherein isotonic water and phosphate buffered saline read on a pharmaceutically acceptable carrier) (column 6, lines 30-40). When the pΔRC-pp65 and pTet-gB were inoculated separately into two different legs, 4 out 6 mice tested developed pp65-specifc CTL response (column 13, lines 14-25). These results establish that; 1) pp65-specifc CTL responses are induced after immunization; 2) there is no antigenic competition between gB and pp65 proteins in the induction of antibody and CTL responses; 3) gB protein expression in the cells at the inoculation site does no interfere with the presentation of pp65-specifc T cell epitopes by the MHC class I molecules (column 13, lines 20-25). Moreover, Gonczol et al, teaches pΔRC-gB_{680}, mixed with pΔRC-pp65 and given at one site or inoculated separately induce both gB- and pp65-specifc antibodies (column 16, example 13). Gonczol et al, provides DNA molecules useful for in vitro and in vivo expression of antigenic fragments of the HCMV genome. Antigens include full-length and transmembrane-deleted fragments of gB such as gB.sub.1-680, pp65, pp150, and IE-exon-4. The DNA molecules of the invention are plasmids (column 3, lines 9-15). The inventors have found that these DNA molecules induce HCMV-specific immune responses, including neutralizing antibodies and cytotoxic T lymphocytes (CTL), and are further useful in priming immune responses to subsequently administered HCMV immunogens and vaccines (columns 12-20, examples 9-14). Gonczol suggests that there remains a need in the art for additional compositions useful in preventing CMV infection by enhancing immune responses to HCMV vaccines and generating neutralizing antibody and/or cellular responses to CMV in the human immune system (column 1, lines 47-52). **Gonczol et**

al, differs from the claimed invention by not teaching a composition comprising of gB, pp65 in combination with gcII (glycoprotein M (gM) complex for the development of a HCMV vaccine.

However, at the time the claimed invention was made, **Mach et al,** teach a complex formation by human CMV gM and gN (title). Mach teaches that a complex formation was required for transport of the proteins from the endoplasmic reticulum to the Golgi and trans-Golgi network (TGN) compartment (abstract). Mach teaches that sera from HCMV-seropositive donors tested positive for the gM-gN complex but negative for either gM or gN alone (abstract). Mach discusses that the maturation of the gM-gN complex occurred in the distal compartment of the protein secretory system and which is believed to be the cytoplasmic site of virion assembly in HCMV-infected cells (p 118891, 1st column, 1st paragraph). Mach suggests that the gM-gN complex may represent a major antigenic target for antiviral antibody responses and a highly immunogenic structure for the humoral immune response during natural infection (p 11882, 1st column, 2nd paragraph). Mach discusses that the potential importance of this response to the gcII (gM-gN) complex indicates that the majority of the infected newborns lack detectable antibodies against the gcII complex, whereas most adult convalescent-phase sera contain gcII-specific antibodies (p 11891, 1st column, 2nd paragraph). Mach suggests that future experiments will be directed towards defining the functional and immunological properties of the gM-gN complex (p 11891, 1st column, last paragraph). As such Mach provides sufficient motivation for one of ordinary skill in the art to apply the plasmid technology of Gonczol to induce the neutralizing antibody response comprising gB, pp65 in combination with gcII for vaccine development.

Accordingly, in view of the teachings of Mach, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the gB, pp65 plasmid technology of Gonczol by including a gcII palsmid for a vaccine development with a

reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification as Gonczol have suggested that it remains a need in the art for additional compositions useful in preventing CMV infection by enhancing immune responses to HCMV vaccines and generating neutralizing antibody and/or cellular responses to CMV in the human immune system.

Temperton supplements the teachings of Mach by teaching that the HCMV infects up to 2,4% of children born in different countries, that there is 1% chance that pregnant women who are sero-negative will develop a CMV infection and that the majority of individuals who are infected with CMV have an immature immune system or are immuno-impaired (p 169, 1st paragraph). Further, Temperton teaches that developing a HCMV vaccine is a major public health priority.

Accordingly, in view of the teachings of Temperton it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the teachings of Gonczol and Mach by administering the vaccine composition to individuals with immature or immunoimpaired immune systems and pregnant women who are sero-negative in order to prevent HCMV infection. One of ordinary skill in the art would have been sufficiently motivated to make such a modification to use the vaccine composition by Gonczol and Mach in order to address the major public health problems caused by CMV infections. One of ordinary skill in the art would have a reasonable expectation of success because the vaccine composition taught by Gonczol and Mach is effective at inducing immune responses in mice.

Thus, the claimed invention as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

Claims 7-8, 11, 14, 18, 33, 36-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Gonczol et al,** (US 6,448,389 B1; 2002) in view of **Mach et al,** (Journal of Virology, 11881-11892, 2000); **Temperton** (International Journal of Antimicrobial Agents, 19: 169-172, 2002) as applied to claims 1, 3, 6, 17, 32, 34 above, and further in view of **Theiler et al,** (Journal of Virology, 2890-2898, 2002); Weis et al, (Vaccine, 18: (815-824, 2000).

The 103 rejection of claims 7-8, 11, 14, 18, 33 as being unpatentable over Gonczol/Mach/Templeton is applied here as indicated above.

Gonczol/Mach/Templeton do not teach a HCMV vaccine with inclusion of HCMV gcIII immunogenic composition.

However, at the time the invention was made, Theiler is an exemplified prior art that teaches the gcIII (gH and gL and gO) complex is necessary for the final stage of the virus entry-pH-independent fusion of the viral envelope with the host cell plasma membrane (p 2890, 1st column, 2nd paragraph). Human cytomegalovirus (CMV) glycoproteins H, L, and O (gH, gL, and gO, respectively) form a heterotrimeric disulfide-bonded complex that participates in the fusion of the viral envelope with the host cell membrane. Theiler discusses that during virus maturation, this complex undergoes a series of intracellular assembly and processing events which are not entirely defined. Theiler et al demonstrate that "gO does not undergo the same posttranslational processing in transfected cells as it does in infected cells. We further determined that gO is modified by O-linked glycosylation and that this terminally processed form is highly enriched in virions. However, during studies of gO processing, novel gO complexes were discovered in CMV virions. The newly identified gO complexes, including gO-gL heterodimers, were not readily detected in CMV-infected cells. Further characterization of the trafficking of gO through the secretory pathway of infected cells localized gH, gL, and gO primarily to the Golgi apparatus and trans-Golgi network, supporting the conclusion that the

novel virion-associated gO complexes arise in a post-Golgi compartment of infected cells" (abstract).

Thus, it would also have been obvious for one of ordinary skill in the art of HCMV immunoengic composition to further employ a gcIII complex of choice available in the art in the immunogenic composition of the combined cited reference. One of ordinary skill in the art would have been motivated to employ a gcIII complex in the immunogenic composition in order to effect the efficacy of the immunogenic composition when administered *in vivo.* One of ordinary skill in the art would have reasonably expected that further inclusions of HCMV glycoproteins are routinely employed in the art and can help to further stimulate an immune response against a target molecule of choice particularly in view of the totality of the prior art at the time the invention was made.

Gonczol/Mach/Templeton/ Theiler do not teach HCMV vaccine with the truncated form of gB in association with a tissue plasminogen activator leader sequence.

However, at the time the invention was made, Weiss teaches an improvement of the immune response against plasmid DNA encoding OspC antigen one of the most promising candidates for Borrelia vaccine (abstract). Weiss teaches that immunization with the construct containing the OspC gene undr the transcriptional control of the CMV promoter elicited a marginal response, which was drastically improved by a fusion construct containing the human tissue plasminogen activator leader sequence (abstract and M&Ms). Weiss discusses that s construct containing a heterologous signal sequence trargeting the trnsalted proteins into the secretory pathway overcomes the weak immunogenicity of the original constructs (p 823, 1st column, 3rd paragraph).

Thus, it would also have been obvious for one of ordinary skill in the art of HCMV immunoengic composition to employ a truncated form of gB in association with a tissue

plasminogen activator leader sequence inorder to increase the immunogenicity against CMV of choice available in the art in the immunogenic composition of the combined cited reference. One of ordinary skill in the art would have been motivated to employ a employ a truncated form of gB in association with a tissue plasminogen activator leader sequence in the immunogenic composition in order to effect the efficacy of the immunogenic composition when administered *in vivo.* One of ordinary skill in the art would have reasonably expected that further inclusion of a truncated form of gB in association with a tissue plasminogen activator leader sequence are routinely employed in the art and can help to further stimulate an immune response against a target molecule of choice particularly in view of the totality of the prior art at the time the invention was made.

Thus, the claimed invention was prima facie obvious.

Claims 1, 34-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Gonczol et al,** (US 6,448,389 B1; 2002) in view of **Mach et al,** (Journal of Virology, 11881-11892, 2000); Weis et al, (Vaccine, 18: (815-824, 2000) and further in view of **Endresz et al,** (Vaccine 17: 50-58, 1999).

The Gonczol/Mach/Weiss teaching is applied here as indicated above. **Gonczol/Mach/Weiss** differs from the claimed invention by not teaching a composition, wherein the gB expresses a truncated form of gB in association with a tissue plasminogen activator leader sequence.

However, at the time the invention was made, **Endresz** is an exemplified prior art that teaches a vaccine composition comprising a gB and pp65 of the HCMV (M&Ms). Endresz teaches immunization of mice with this composition raised an antibody response to both proteins and induced a pp65-specific CTL response (abstract and M&Ms). Endresz teaches

that the HCMV gB secreted form is more immunogenic than the membrane-bound full-length gB (p 56, 2nd column, 1st paragraph).

Thus, it would also have been obvious for one of ordinary skill in the art of HCMV immunogenic composition to further employ a leader sequence of choice available in the art such as a tissue plasminogen activator leader sequence in the immunogenic composition of the combined cited reference. One of ordinary skill in the art would have been motivated to employ a leader sequence in the immunogenic composition in order to effect the efficacy of the immunogenic composition by producing the secreted form of gB. One of ordinary skill in the art would have reasonably expected that further inclusions of leader sequences for secreted glycoproteins are routinely employed in the art and can help to further stimulate an immune response against a target molecule of choice particularly in view of the totality of the prior art at the time the invention was made.

Thus, the claimed invention was prima facie obvious.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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